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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/289,346	04/09/99	HANLEY-BOWDOIN L	5051-458

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EXAMINER	
DRABIK,C	
ART UNIT	**PAPER NUMBER**
1633	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/289,346	Applicant(s) HANLEY-BOWDOIN ET AL.	
	Examiner Christopher Drabik	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 42-55 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 42-55 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

Detailed Action

The disclosure is objected to because of the following informalities:

1.) Figure 8 is referred to in the specification, however, no figure 8 is provided in the disclosure.

2.) There appears to be an error in table 6. The data provided in table 6A does not seem to correlate with the data in 6B.

Appropriate correction is required.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 42-49 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 42 recites: "...(b) a nucleic acid sequence encoding a mutant AL1 protein,..." Subsequently the claim reads "...and comprising a mutation in the Rb binding region,..." It is unclear to the examiner how many mutations are being recited in the claim. Further it is not apparent exactly where the location of mutations might reside, other than the mutation claimed within the Rb binding region. Claims 43- 48 depend from claim 42 and, hence, claims 43-48 are subject to the limitations of claim 42.

Claims 45 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 45 recites the limitation " wherein said trans-dominant negative mutant Al1 protein". There is insufficient antecedent basis for this limitation in the claim. Claim 45 depends from claim 42. Claim 42 is an independent claim with no limitations cited regarding a trans-dominant negative mutation. Therefore, no precedent for claiming "said trans-dominant negative mutant Al1 protein" in claim 45 has been established.

Claims 45 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 45 is drawn to a nucleic acid construct ..."wherein said...mutant protein has a mutation in a domain selected from..." As, the claim is worded, it is unclear whether the mutant protein has one, two or multiple mutations. The mutation selected from the groups denoted in claim 45 may be the defining element which makes the protein a mutant or, alternatively, the mutation selected from the groups may be in addition to an existing mutation. It is unclear which particular construct the applicants mean to claim.

Claim 46 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 46 is drawn to a nucleic acid sequence encoding ... "an AL1 protein with increased repression of transcription from the AL1 promoter, compared to a wild type AL-1 protein." This claim is unclear because the promoter of the wild type

AL1 sequence is independent from the sequence of the protein. It is unclear whether the Al1 protein has the capability of "increased repression of transcription" or the nucleic acid construct has "increased repression of transcription". It is not apparent whether the Al1 nucleic acid construct exhibits "increased repression of transcription " because the promoter is less efficient from other promoters or the protein encoded by the nucleic acid construct is more efficient at reducing transcription, or both. Applicant should amend the claim such that it is clear that applicant means mutant Al1 protein binding to the Al1 promoter or reduced transcription rates of Al1 based on promoter differences.

Claim 47 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 47 recites the limitation "said plant" in. There is insufficient antecedent basis for this limitation in the claim.

Claim 48,49 and 55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 48,49 and 55 refer to **nucleic acid** sequences listed as SEQ IDS 1-10. No such nucleic acid listings are provided, rather the sequence listings provided are for amino acids. The claims should be amended such that they are in concordance with the provided sequence listings

Claim 49 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 49 recites: "...(b) a nucleic acid sequence encoding a mutant AL1 protein,..." Subsequently the claim reads "...and comprising a mutation in the Rb binding region,..." It is unclear to the examiner how many mutations are being recited in the claim. Further it is not apparent exactly where the location of mutations might reside, other than the mutation claimed within the Rb binding region.

Claim 50 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 50 recites: "... (a) a promoter operable in said plant cells,..." Claim 50 is an independent claim with no mention of a plant cells prior to the recitation "said plant cells", therefore, no antecedent basis is provided for the recitation "said plant cells."

Claim 55 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 55 recites: "...(b) a nucleic acid sequence encoding a mutant AL1 protein,..." Subsequently the claim reads "...and comprising a mutation in the oligomerization region,..." It is unclear to the examiner how many mutations are being recited in the claim. Further it is not apparent exactly where the location of

mutations might reside, other than the mutation claimed within the oligomerization domain.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 42-55 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed."Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

Claims 42-55 are drawn to a nucleic acid constructs comprising a plant operable promoter, mutant AL-1 encoding sequence and transcription termination sequence, said nucleic acid constructs comprise at least a mutation in the Rb-binding region, said nucleic acid constructs can be part of a plant transformation vector, said constructs can comprise mutations in the AL-1 coding region such that the mutation has a trans-dominant negative effect on geminiviral replication, said nucleic acid constructs can also

comprise mutations in the oligomerization, DNA cleavage, or ATPase domain. In addition, said nucleic acid constructs can encode AL-1 proteins with increased repression of transcription from the AL-1 promoter and said nucleic acid sequence can comprise nucleic acid SEQ IDS 2-10.

The scope of the claims encompasses mutations in the Rb binding region of any and all Al-1 proteins in any and all geminiviruses. The specification seems to indicate that the group of proteins described as Al-1 proteins also encompasses any and all Rep and C1 proteins. The scope of the claims encompasses nucleic acid constructs encoding AL-1 proteins mutated in the Rb binding domain and also comprising all mutations which have a trans-dominant negative effect on processes of geminiviral infection. In addition, the claims encompass nucleic acid constructs encoding AL-1 proteins mutated in the Rb binding domain and comprising mutations having the effect of increased repression of the AL-1 promoter compared to wild type Al-1 protein – transcriptional repression.

While the specification provides adequate written description for the generation and use of nucleic acid constructs comprising mutations in the Rb- binding domain of TGMV, the specification does not provide adequate written description for the generation of mutations effecting AL-1 – Rb-binding in any and all geminiviruses. In particular, written description is lacking for mutations in which the Rb binding motif differs from the motif found in TGMV. While the scope of the claims encompass LXCXE amino acid motifs, an exemplary Rb- binding motif present in other geminiviruses, no written description for mutations in the LXCXE motif is provided. At the time of filing, interactions of Rb with AL-1 proteins was as yet incompletely defined. The structure of the Rb-binding domain in TGMV AL-1 is novel and binding of Rb to other AL-1 proteins, not having the LXCXE motif, had not been disclosed. Based on the limited evidence for

binding of Rb to other TGMV-like AL-1 proteins, it is not possible for one skilled in the art to envision any and all mutations in any and all AL-1 proteins such that one skilled in the art would know that the inventors had possession of the invention at the time of filing. The skilled artisan cannot envision the detailed chemical structure of all of the encompassed Rb binding elements isolated from any and all AL-1 proteins and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method

Regarding written description of trans dominant negative mutants, the specification clearly indicates a limited number of TGMV AL-1 nucleic acid constructs comprising mutations in the DNA cleavage, DNA binding and oligomerization domains wherein said mutations have trans-dominant negative effects on geminiviral replication in transient transfection assays at three days post transfection. The specification does not provide sufficient description such that one skilled in the art could know the inventors had possession of any mutations outside of the domains limited to the oligomerization DNA binding and DNA cleavage domain which can produce trans-dominant negative effects. In particular, ***no description of trans-dominant negative mutations in the TGMV AL-1 ATPase domain are provided*** and, significantly, the region of the DNA cleavage domain described adequately comprises only a minor fraction of the entire cleavage domain.

The scope of the claims also encompass any and all AL-1 proteins having the mutations in the Rb binding region and also comprising any and all mutations effecting increased repression of transcription relative to the capability of wild type TGMV AL-1. Written description is provided for mutations in TGMV AL-1 within amino acids 118 to 179 which show increased levels of transcriptional repression in a luciferase reporter assay. Mutations external to amino acids 118 to 179 resulting in increased

transcriptional repression is not provided. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants effective filing date. In the instant application, mutations of TGMV-AL-1 external to amino acids 118-179 yielding increased transcriptional repression of the AL-1 promoter are not addressed and hence, the specification does not provide sufficient written description commensurate with the scope of the claims.

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). Therefore, only the described mutant Rb binding sequences of TGMV AL-1 meet the written description provision of 35 U.S.C. §112, first paragraph.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 42-55 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acid sequences coding for specific mutations in the Rb-binding and oligomerization domains of TGMV AL1 does not reasonably provide enablement for AL1 mutations in the Rb-binding and oligomerization

domains proteins of all species of geminivirus. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 42-55 are drawn to nucleic acid constructs coding for AL-1 proteins comprising a mutation in the Rb binding domain, said protein also/alternatively comprising mutations in the oligomerization domain, DNA cleavage domain or the ATPase domain, said nucleic acid construct also comprises expression cassettes comprising plant operable promoter and termination sequences. The specification describes TGMV AL-1 coding sequences important to binding maize Rb protein and coding sequences important to oligomerization of the AL-1 protein. The scope of the claim encompasses mutations of all Rb binding and oligomerization domains of AL-I proteins from all Geminiviruses.

A significant aspect of invention as claimed is the ability or decreased ability of the protein coded for in the nucleic acid sequence to bind a plant analog to of the Rb – like proteins. The family of Rb-like proteins are widely found in metazoan species and are important to the proper functioning of the cell cycle. A considerable exception is the lack of an Rb-like protein in yeast. Despite significant effort to identify the gene in yeast no such protein has been yet discovered. The state of the art indicates that until recently it was believed that the Rb-like proteins did not exist in plants. (Durfee et al (2000) Plant Mol Biol 43:635-642 p 636 col 1, 2nd full paragraph), however within the past several years genes encoding Rb-like proteins have been cloned from Zea mays, Niciotiana tabacum and Arabidopsis thaliana. Proteins interacting with the Rb-protein have been

characterized as containing the conserved binding motif LXCXE. (Dahiya et al (2000)Mol Cell Biol 20:6799-6805, Picksley SM et al (1994) Curr Op Cell Biol 6:853-858, Williams, L et al (2000) Trends in Plant Science vol 5 no 6 239-40).

The LXCE binding motif has been described in the geminivirus wheat dwarf virus and is conserved in most, but not all mastreviruses. The motif is found in the Rep A protein and has been shown to interact with human and plant Rb-like proteins. (Reviewed in Gutierrez, C (2000) Plant Mol Biol 43:763-772 see page 768). Binding of plant Rb proteins to AL1 protein of TGMV have also been described. (Ach, R et al (1997) Mol Cell Biol 17:5077-5086), however the binding region is novel in that it does not contain a canonical LXCXE motif and the TGMV Al-1 sequence involved in binding has apparently not been previously disclosed. Furthermore, Rb binding to AL-1 proteins of other begemoviruses has not been described.

While applicant has disclosed the sequences, and mutations thereof which involve the TGMV AL-1 protein's interactions with maize Rb protein, the scope of the invention claims to enable Al-1 sequences from the geminiviridae and that group of proteins interaction with all Rb proteins. Given that it has been established above that Rb protein is not limited to binding to one protein motif, applicant has not provided enablement for determining all possible Rb binding sequences within the group of Al-1 proteins capable of binding Rb, Furthermore, Applicants have also not provided the means for establishing reduced binding of Rb to any other AL-1 protein other than the Al-1 protein of TGMV.

The oligomerization domain of TGMV has been characterized by members of the inventive entity in some detail (see the instant application and e.g. Orzoco et al (2000) JBC 275: 6114-6122). Furthermore, trans-dominant negative mutations of the AL1/Rep/C1 protein have recently been generated by other researchers, however, the mutations in these constructs were in the NTPase domain of the AL1/Rep/C1 protein. (Noris, E et al (1996) Virology 224: 130-138). Apparently unique to the instant application is the indication that specific mutations within the oligomerization domain of the TGMV AL-1 protein can be generated to produced a dominant negative effect on the infective process of TGMV in co-transfection experiments. Another unique aspect of the constructs as claimed has to do with mutations concomitantly involving the Rb binding region and oligomerization domain of TGMV AL-1.

The most thoroughly characterized oligomerization domain in the literature is the domain present in TGMV. Limited information regarding other geminivirus oligomerization domains exist and, apparently, it is as yet unclear as to whether all oligomerization domains of other geminiviruses map to similar sequences (Orzoco et al 1995 p 6219 2nd column, last paragraph). Orzoco et al compares the predicted amino acid sequences of the TGMV oligomerization domain and similar sequences of a number of other geminiviruses. (Orzoco et al, 1995 p 6120, figure 7) While significant amino acid residue conservation occurs within the begomoviruses, amino acid homology to TGMV drops considerably in the mastreviruses. This suggests that the mastrevirus sequences, if they in fact are oligomerization domains, may have other critical moieties.

Based upon the breadth of the claim, the lack of direction provided by the applicants, and the unpredictability of the art, the invention(s) of claims would require undue experimentation for one skilled in the art to practice commensurate with the scope of the claims and are, therefore rejected as not meeting the criteria of 35 USC 112, first paragraph.

Conclusions

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher Drabik whose telephone number is 703-605-1156. The examiner can normally be reached on Monday-Friday from 9am to 5pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on 703- 305-4051. The fax phone number for the organization where this application or proceeding is assigned is 703-308-4242.

Inquiries of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234. Questions regarding review of formality issues may be directed to Kim Davis, the patent analyst assisting in this application. She may be reached at 703-305-3015.

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